EXHIBIT 1

Page 114

Do you see that?
A. The figure legend says that, yes.
Q. And that would be small intestine because you see villi, right?
A. It's small intestine. Histologically I can't confirm that it's proximal because specific features of proximal small intestine aren't present in this image, but I can take their word for it.
Q. And if you compare that image to what is shown on the prior page, do you agree with them that this shows improvement in the histological picture of the villi?
A. With the recognition that celiac-like diseases are patchy, yes.
MR. SLATER: Move to strike before the word "yes."
Q. I just want to understand one thing. When you say that celiac-like diseases are patchy, you would include olmesartan-associated enteropathy in that, correct?
A. I think we've been over this. No.
Q. Is that because you don't believe olmesartan-associated enteropathy exists as an

Page 115

entity?
A. I don't think it's been definitively shown to be true, to be an entity.
Q. If the people -- I'd like you to assume -- a hypothetical. I'm going to ask you a new question. I'd like you to assume that the people who believe olmesartan-associated enteropathy is a real clinical entity are correct and that you're wrong, I'd like you to assume that, okay?
A. Okay.
Q. Assuming that to be true, there is evidence that it has a patchy appearance on biopsy, correct?
A. I believe that's what's been reported.
Q. Looking at Exhibit 9, this letter from Drs. Gallivan and Brown, in the last paragraph they state in the second sentence, "Thus, it is important to consider olmesartan induced enteropathy in patients with histological sprue-like findings, with or without colonic inflammation, in the absence of other celiac disease or other medical condition."
Do you see that?

Page 116

A. Yes.
Q. You agree with that statement in terms of that clinicians should consider olmesartan induced enteropathy under those circumstances, correct?
A. For the reasons we discussed, I wouldn't agree with the phraseology. I would agree that you'd want to consider taking your patient off olmesartan if they failed a gluten-free diet and have appropriate histopathology, and so on.
Q. The reason that a clinician would take a patient off of olmesartan in the setting of the clinical features of sprue-like enteropathy is because the clinician thinks that the olmesartan may be causing the clinical syndrome, correct?
A. They recognize it as a possibility, yes.
Q. And where the only change that's made is the withdrawal of the olmesartan in a particular patient, and the patient's clinical syndrome resolves, the symptoms go away, the pathology normalizes, in that case, all other

Page 117

things being equal, olmesartan-associated enteropathy should be on the differential diagnosis as the cause of that clinical presentation, correct?
MR. PARKER: Objection.
A. I think permanent withdrawal of olmesartan in their drug regimen would be a reasonable practice.
BY MR. SLATER:
Q. And the reason why it would be reasonable to permanently withdraw the olmesartan is because, and we'll start small here, of the possibility that the olmesartan was causing the clinical syndrome, correct?
A. Sure, that remains a possibility.
Q. Where the only change made is the withdrawal of the olmesartan, and the patient then has resolution of the clinical symptoms and the pathology normalizes, in the absence of any other change for that patient, the olmesartan is the likely cause of the clinical syndrome that was being suffered by patient, correct?
MR. PARKER: Objection.
BY MR. SLATER:

Page 118

Q. From a clinical perspective for that patient, correct?
A. That would indicate a correlation, and a good management decision in the patient. It does not indicate that olmesartan caused that.
Q. It indicates that olmesartan, from a clinical perspective, was the likely cause of the clinical symptoms that ceased and normalized and got all better when the patient stopped taking the olmesartan if it was the only change that the patient had, correct?
A. Again, I --
Q. Clinically.
A. I think clinically it tells you that it would be a good idea to change the medication regimen for that patient. You can theoretically say maybe it was the cause, let's not give this patient olmesartan. But I don't think you can conclude that olmesartan was the cause.
Q. Is it your testimony the only way that you can conclude the olmesartan was the cause if you then were to put the patient back on the olmesartan, and the symptoms and the pathology were to recur?

Page 119

A. You know, you really need -- in these sorts of cases we know the placebo effects can be strong, you really need controlled tests. That's really the only way to do it. Really case reports are the weakest form of data in the medical literature, that's well-recognized throughout the medical literature, you really can't draw these conclusions from uncontrolled case reports like this.
Q. So you're saying that you'd need to see a controlled rechallenge to prove causation in that case, right?
MR. PARKER: Hold on. Technical problem.
A. I'm saying we need a controlled and properly done randomized rechallenge, and then you can make a determination about one patient.
BY MR. SLATER:
Q. If it causes it in one patient, then that would answer the question that there is general causation, correct?
MR. PARKER: Objection.
A. If it causes it in one patient by some idiosyncratic reaction where it unmasks a

Page 120

disease in that patient, then it may not be general causation, it may just be a trigger.
BY MR. SLATER:
Q. Are you aware whether any of the patients in the ROADMAP Trial had dechallenges and rechallenges that were positive?
A. I'm not aware of any rechallenges in the ROADMAP Trial.
Q. If the patient in my hypothetical to you that we were just talking about had a controlled rechallenge and the clinical symptoms were to recur, then in terms of what's more likely than not, from a clinical perspective it would be more likely than not to say the olmesartan was causing that condition, correct?
A. A blinded control rechallenge, then I would say yes.
Q. The reason that you say a blinded controlled rechallenge is for what reason? Why do you use that as your standard?
A. Because we know that the placebo effect is very strong, and that it's been demonstrated in study after study. And so if you tell the patient now I'm going to give you

Page 121

olmesartan, let's see if things recur, and the patient in their mind is believing that olmesartan caused that, without intentionally lying or any other intended deceit, the patient may experience those symptoms.
Q. Any other reason?
A. No, it's really we need to eliminate placebo effect as a cause.
Q. Okay. Can you tell me any published article in the olmesartan literature that gives the opinion that you just gave, that the only way to prove causation is through a blinded controlled rechallenge that shows a positive rechallenge? Can you point to any peer-reviewed article that actually has that?
A. I don't think anybody has discussed the issue of how would you really prove this rigorously, so no.
Q. The Exhibit 9, the letter from Drs. Gallivan and Brown is published in a journal called Pathology. Is that a respected medical journal?
A. I think I've heard of it. It's certainly not one of the better pathology

Page 122

journals.
Q. What are the high powered journals that you would say are the ones that you can respect what they publish?
A. In pathology specifically?
Q. Let's start pathology.
A. Annual Review of Pathology Mechanisms of Disease, Journal of Pathology, American Journal of Pathology, perhaps Laboratory Investigation, Nature Medicine will address pathology sometimes, American Journal of Surgical Pathology for a subset of entities.
Q. Any others?
A. That's a pretty reasonable list. You might include Modern Pathology for certain things, not really clinical trial type stuff, so not in this context, but Modern Pathology can be reputable.
Q. Are you aware that in the Mini-Sentinel that was performed by the FDA that they identified 23 cases of what they believed to be olmesartan-associated enteropathy, 10 of which had rechallenges?
MR. PARKER: Objection.

Page 123

A. I'm looking for the exact number. Yes, I'm aware in general that in the Mini-Sentinel there were cases with these same sorts of case report rechallenges that we've been discussing.
Do you want me to find the exact numbers?
BY MR. SLATER:
Q. I asked you if you're aware that 10 of the 23 patients were stated by the FDA to have positive rechallenges?
A. I can't confirm that number.
Q. Does it sound correct to you?
A. Sorry, I've read a lot of literature for this. I'm trying to remember exactly what this said.
(Witness reviewing document.)
A. You'll have to tell me where it specifies the rechallenge cases. I'm not seeing it in looking through it briefly here.
BY MR. SLATER:
Q. Assuming -- I'll find it at some point.
But assuming that I'm correct that of

Page 124

the 23 cases identified by the FDA, 10 of them had positive rechallenge, that is significant evidence supportive of the proposition that olmesartan causes sprue-like enteropathy, correct?
A. It certainly causes you to want to investigate further, absolutely.
Q. In fact, if you put evidence in a scale, on one side is supportive of causation and on the other side is evidence that cuts against causation, the positive dechallenges and positive rechallenges reported in the literature, they all weigh on the side of supporting the opinion that olmesartan causes this condition, correct?
A. Correct.
Q. You know what, actually I do have it here.
A. Great.
Q. So let's do this to be fair to you. Peter, can you go to document 8? It's an article by Marietta, Cartee, Rishi and Murray.

Page 125

(Whereupon, Turner Exhibit Number 10, Marietta, et al article titled Drug-Induced Enteropathy, was marked for identification.)
BY MR. SLATER:
Q. Doctor, do you see this article? Are you familiar with this?
A. I am.
Q. Okay. And let's look, to begin with, at the title, "Drug-Induced Enteropathy."
Do you see that?
A. Yes.
Q. Would you agree with me that as the authors use that term in this article, when they use the word "induced," they're using it synonymously with caused by?
A. I think they probably are.
Q. And just to start off, go to Page 217, the right-hand column just above the heading that says "Treatment," it says, "The Mini-Sentinel study on olmesartan and celiac disease by the FDA found 10 of 23 patients had a positive rechallenge."
Do you see that?

Page 126

A. Yes.
Q. That is evidence that supports the argument for causation, correct?
A. Sure.
MR. PARKER: Objection.
A. Yes, that would be on the in favor of causation side of the balance.
BY MR. SLATER:
Q. Let's look at the very beginning of this article on the first page in the Abstract section. It says, "Many medications can cause diarrhea by increasing motility, inflammation or enteropathy."
Do you agree with that statement?
A. Yes.
Q. And this is published in Digestive Diseases. Is that a respected medical journal?
A. Not really.
Q. Do you respect Dr. Murray? I think you said before he's one of the world's authorities in this field, right?
A. I respect Dr. Murray. I was asked to be an associate editor of Digestive Diseases and declined. It's not really a great journal.

Page 127

Q. Dr. Murray is one of the world's authorities on this issue, correct?
A. On celiac disease, absolutely. Is that what you're asking?
Q. And do you know -- and you've actually co-authored a publication with Dr. Murray, is that right?
A. I think we're co-authors of a publication, might be two.
Q. The second sentence in the abstract -- I'm sorry, did I interrupt you?
A. Yeah. I was going to say there might be more than one that I'm co-authors with Joe on, but I'm not certain.
Q. Okay. Have you ever told him that you think he publishes in garbage medical journals?
A. You know, I think probably everybody has published papers in garbage medical journals from time to time. And I think if I told him maybe not in such crude terms that I thought this was not really the best journal, I think he'd agree.
Q. Are very good articles with very good science published in garbage medical journals

Page 128

sometimes?
A. They can be. This is really a review more than anything, so this isn't even original article with particular data.
MR. SLATER: Move to strike after "they can be."
Q. Let's look now at the second sentence of the abstract. "Olmesartan and mycophenolic acid (CellCept) are drugs that are capable of increasing inflammation in some individuals and, if not recognized, can lead to chronic diarrhea."
Do you agree with that sentence?
A. I agree that that's what's written.
Q. Do you agree that that statement is accurate?
A. No.
Q. In this type -- rephrase. The next sentence says -- I'll withdraw that. Okay.
You agree with me that the prevailing opinion in the peer-reviewed medical literature is that the sentence I just read to you is an accurate statement, correct?
MR. PARKER: Objection.

Page 129

A. I think many people have said that it's associated. I think that demonstration that it's capable of increasing inflammation and enteropathy is not well established.
BY MR. SLATER:
Q. The majority of articles that have addressed the question and state either directly or indirectly whether there's causation, the majority do indicate that olmesartan can cause this condition, correct?
A. I'd have to count them. I think some with a lack of scientific rigor state that. I don't know if it's equal or not. I know, for example, that the 2012 Rubio-Tapia article we were discussing takes careful lengths not to say that.
MR. SLATER: Move to strike.
Q. Let's go to the conclusion of this article. The conclusion states, "The drug-associated enteropathy that is most common and serious is that seen with olmesartan, albeit at an extremely low rate."
Is that a true statement?
A. I think there's an association in some

Page 130

patients with olmesartan, as we've been over. I don't know if I'd agree that was most serious. I think I've seen patients on ipilimumab, which is discussed here, and mycophenolate who are pretty ill, so maybe.

Q. Is Dr. Murray an expert regarding the clinical manifestations and treatment of olmesartan-associated enteropathy?

A. I think he's probably published more than anybody on it, if that's your question.

Q. And you've -- rephrase.

You've read his articles, and you see he's been involved in the treatment of many patients with this condition, correct?

A. With what he refers to as olmesartan-associated enteropathy, absolutely. I also see that he's really careful not to say it's caused.

Q. And just to be clear, you've never been involved in the evaluation or treatment of any patient where an olmesartan-associated illness was a part of the patient's clinical picture, or even considered, right? You've never been involved with that, right?

Page 131

A. Right.

Q. Dr. Murray states in the second -- rephrase.

The second sentence states, "One should then suspect olmesartan-associated enteropathy in any patient who presents with severe diarrhea and weight loss. Many of the features associated with olmesartan-associated enteropathy are also found in the enteropathy found in celiac disease; because of this, one should review any celiac disease diagnosis for any use of olmesartan at the time of diagnosis. Features that are usually found in olmesartan-associated enteropathy but are not found in celiac disease are collagenous sprue, colitis, and gastritis. Finally, one should consider the possibility of other ARBs inducing enteropathy as there are case reports of valsartan and irbesartan associated with enteropathy."

Do you see where I just read?

A. Yes.

Q. I want to start with the last sentence first. Do you agree with that sentence?

Page 132

A. That there are case reports? Yes.

Q. Do you agree with the clinical recommendation that's given in that sentence?

A. Sure, can't hurt.

Q. Do you have an opinion as to whether there's a class effect for ARBs inducing enteropathy?

A. I don't.

Q. Let's look now at the sentence -- rephrase.

Looking at what I just read up to but before the last sentence, that is a clinical recommendation from these authors, correct?

A. Not entirely.

Q. There are clinical recommendations in that section that I just read, correct?

A. The sentence begins "One should then suspect." That sentence is a clinical recommendation. The rest is not.

No, there's -- second half of the next sentence also is a clinical recommendation. Excuse me.

Q. You agree that it makes sense and is reasonable for clinicians to be vigilant and

Page 133

aware of olmesartan-associated enteropathy in evaluating patients with clinical presentations that have the features of sprue-like enteropathy, it's reasonable for them to consider that as part of their differential, correct?

A. I think given that these reports exist, it would be reasonable to consider that, absolutely.

Q. And when a physician takes the patient off the olmesartan and they improve or have their condition completely resolved, it's reasonable to keep the patient off the olmesartan, correct?

A. Since as a physician your goal is to make your patient feel better and have better health, the answer would be yes.

Q. And when a patient makes that type of decision, they're considering the concept of cause and effect in determining whether or not to hold the medication and give a new medication permanently, or whether to put the patient back on the medication, right?

MR. PARKER: Objection.

Page 134

A. In clinical terms.
BY MR. SLATER:
Q. If the physician then says to the patient, okay, you seem like you're better, let's put you back on the olmesartan, and the patient has the clinical symptoms recur, you would agree at that point it's very reasonable for the physician to say, I'm going to pull you back off the olmesartan and we're going to find a different medication for your high blood pressure?
A. Sure.
Q. That's a reasonable clinical decision, right?
A. That's a completely reasonable clinical decision.
Q. And if the physician were to make that decision based upon their clinical judgment that the olmesartan was causing the condition, that would be a reasonable clinical judgment based on those facts, correct?
A. I think you have to ask what you're implying there. If you're implying causation in the scientific or legal sense, no, they don't

Page 135

have sufficient data to say that. If you're implying in a very loose sense that it might cause it in this patient, it seems like whenever this patient is off olmesartan they're better, we should just use something else because there's not much harm to that, then they can think about it in any terms they like.
MR. SLATER: Well, move to strike.
Q. My question is very specific. If the doctor told the patient, you got better when we took you off the olmesartan, you got sick again when we put you back on the olmesartan, I think that the olmesartan is causing your condition so you should use a different hypertension drug, and you shouldn't take the olmesartan anymore, based on that clinical picture in that clinical context, that's a reasonable medical judgment by that physician, correct?
MR. PARKER: Objection. Asked and answered.
A. I think with some paraphrasing that's correct. I think it might be more appropriate to say I think there's a chance that it's causing that, let's put you on something else

Page 136

rather than I think it absolutely is. So it depends how you deliver that. But in general terms, yes.
MR. SLATER: I just want to ask you guys, I'm just planning, what time do you want to eat lunch? I don't want to burn a lot of time on lunch discussion, I just want to know what time you're thinking of breaking.
MR. PARKER: Any time you'd like to, Adam. It's your deposition.
MR. SLATER: All right. Then I'm just going to keep on going until you guys say -- cry uncle.
MR. PARKER: What time would you like to eat? We're good for a little bit, right?
THE WITNESS: Yes.
MR. SLATER: I might get sent to my room, but that's about it.
MR. PARKER: That's all right.
A. Can we take a break for a minute just to get more coffee?
MR. SLATER: Sure. Go off the video.
THE VIDEOGRAPHER: Going off the record. The time is 11:51.

Page 137

(Whereupon, a recess was taken.)
THE VIDEOGRAPHER: Back on the record. The time is 12:01.
(Whereupon, Turner Exhibit Number 11, Freeman article titled Drug-induced Sprue-like Intestinal Disease, was marked for identification.)
BY MR. SLATER:
Q. Doctor, I'm showing you an exhibit we've marked -- what exhibit did we say we are up to actually?
THE STENOGRAPHER: 11.
BY MR. SLATER:
Q. Doctor, I'm showing you what we've marked as Exhibit 11 titled" Drug-induced Sprue-like Intestinal Disease" published in the International Journal of Celiac Disease.
Do you see this article?
A. Yes.
Q. Are you familiar with this?
A. I think so. I'm not 100 percent sure. I'd have to look at my list. I think I am.
Q. Okay. The International Journal of Celiac Disease, is that a reputable journal?

Page 138

A. I've never heard of it. It looks like it's from one of these predatory publishing companies published outside Pub.com. It looks like it's from one of these sort of predatory publishing companies.
Q. Okay. Let's look --
A. It's a brand new journal. It's just volume two. I don't know.
Q. So someday maybe you'll publish something in it and lift their credit.
MR. PARKER: Maybe so.
A. Hopefully.
BY MR. SLATER:
Q. You know you should send in an article, getting deposed on drug-induced sprue-like enteropathy.
MR. PARKER: Let's go.
BY MR. SLATER:
Q. I'm sure it will be of great interest to the readership. We can send the deposition transcript in to them and they can take excerpts and publish it.
A. If you'd like to pay the page charges, you're welcome to.

Page 139

Q. Okay.
A. I'm sure that they charge high page charges in this journal.
MR. TURNER: Let's go, guys.
BY MR. SLATER:
Q. Okay. At the very start of the article there's a sentence that starts, "Celiac disease (also termed gluten-sensitive enteropathy or celiac sprue) is a gluten-dependent small intestinal disorder seen in genetically-predisposed individuals resulting from a complex immune-mediated reaction to specific gluten-peptides in wheat and other grain products. The precise precipitating event is not known."
Just in terms of that general statement about celiac disease, is that accurate?
A. I think that's accurate.
Q. Turn forward, if you could, to Page 51. There's a section on "Non-steroidal Anti-inflammatory Agents."
Do you see that?
A. Yes.

Page 140

Q. It starts out, "Some nonsteroidal anti-inflammatory agents have been well documented to cause mucosal toxicity, particularly in the stomach and small intestine."
Is that a factually accurate statement?
A. Yes, it is.
Q. If you go to the very end of that paragraph, it says, "Further studies are needed to define the precise mechanism involved for the histopathologic mucosal changes following nonsteroidal anti-inflammatory drug use."
Do you see what I just read?
A. Yes.
Q. And would you agree with that statement?
A. In a sense. I mean there's many mechanisms that have been defined. I don't think it's entirely clear which contribute to which events.
Q. Even though the precise mechanism as they describe it here still needs to be defined, that doesn't take away from the fact that

Page 141

nonsteroidal anti-inflammatory agents can cause mucosal toxicity as described here, correct?
A. Correct.
Q. And in a sense what I'm saying is even though the mechanism is not entirely known, the scientific community accepts that there is a biological mechanism whereby the nonsteroidal anti-inflammatory agents do cause mucosal toxicity, correct?
A. Sure.
Q. And just one quick question about these medications, nonsteroidal anti-inflammatories. They are given to a patient in order to treat inflammation in the body, that's their actual purpose, that's what they do, correct?
A. In general terms, yes.
Q. However, in the small intestine, they can cause inflammation, and actually do in some patients cause inflammation, correct?
A. Again, depending on context, yes.
Q. Okay. So the fact that a medication which has anti-inflammatory properties, that doesn't mean the medication will not cause

Page 142

inflammation in the small intestine as a general proposition, correct?
A. All drugs can have toxicities.
Q. Okay. You can put that aside.
I want to ask you about something we were -- follow up on something we were talking about before. I want to ask you about the Rubio-Tapia patients, the 22 patients in that study, okay?
A. Yes.
Q. With regard to those patients, and I'm not going to go through the full clinical picture and all the histopathologic findings, they're in the article, the article speaks for itself, you're familiar with the article's description of those patients, correct?
A. Yes, I am.
Q. With regard to those 22 patients, it was reasonable for the physicians treating them at the Mayo Clinic to conclude that olmesartan was associated with their -- what was termed their sprue-like enteropathy, their collection of clinical symptoms, correct?
A. I don't think that's exactly correct.

Page 143

Q. With regard to each of those 22 patients, the differential diagnosis would reasonably include olmesartan-associated enteropathy, sprue-like enteropathy, whatever you want to call it, that would be a reasonable thing to do, to include that in the differential diagnosis, correct?
A. Retrospectively, you would include something related to olmesartan as a possible cause, yes. I think when they were seeing these patients, they hadn't thought about that.
Q. They figured it out later when they then got the information that they talked about; for example, patients reporting that when they were in the hospital and were taken off olmesartan because, for example, their blood pressure had gotten lower, that they had gotten better, and that's what essentially triggered these doctors to look more closely at olmesartan, correct?
MR. PARKER: Objection.
A. Yeah, that's fairly simplified, but it's the gist of what they say in the beginning of this article.

Page 144

MR. SLATER: Okay. We have an article, I don't think, Peter, we put a number on it, but it's titled "Celiac Disease" authored by Dr. Green and Dr. Cellier.
A. Is this a New England Journal article?
BY MR. SLATER:
Q. It is.
MR. FOUNDAS: You said it wasn't one of the numbered ones?
MR. SLATER: I don't think it is. If it is, I don't have the number in front of me. Sorry. But it's titled "Celiac Disease," New England Journal of Medicine.
MR. PARKER: Have you got it?
THE WITNESS: I have it.
MR. PARKER: Everybody has got a copy but me.
THE WITNESS: Well, they have to find a copy for me.
MR. PARKER: You hold on to that.
MR. FOUNDAS: Give me a second. Maybe it's in here.
MR. PARKER: This is what you're looking for (indicating).

Page 145

MR. SLATER: Did we not send it?
MR. FOUNDAS: Not through it all yet.
BY MR. SLATER:
Q. Do you have it in the room, Doctor? Maybe I can send it up there.
MR. FOUNDAS: We do have a copy here.
MR. SLATER: The doctor has it?
MR. PARKER: He's got a copy, so let's just go ahead and I'll look at it later.
MR. SLATER: It's not there, let's forget it. I may not have sent it. So as long as you have it, that's the key thing, Doctor.
MR. PARKER: Okay.
MR. SLATER: Let's mark it as whatever the next number is.
(Whereupon, Turner Exhibit Number 12, Green and Cellier article titled Celiac Disease, was marked for identification.)
BY MR. SLATER:
Q. Okay. Doctor, this article is listed on your supplemental reliance list, correct?
A. Yes.
Q. Why did you include it on the

Page 146

supplemental reliance list?
A. I think it's a comprehensive review of celiac disease, and people have likened the pathology and clinical symptomatology associated with diarrhea that's been associated with olmesartan to celiac disease.
Q. Would you consider the New England Journal of Medicine to be a respected medical journal?
A. Yes. We already discussed that.
Q. Have you published in the New England Journal of Medicine?
A. I don't think so. Maybe as a middle author, but I don't think so.
Q. Looking at this article, it says right in the middle of the first paragraph, about five lines down, "Celiac disease is precipitated, in genetically predisposed persons, by the ingestion of gluten." Correct?
A. Correct.
Q. At a very basic level, that is describing the mechanism, that you take gluten and it precipitates this condition, at the very general level, correct?

Page 147

A. No, I wouldn't call that a mechanism.
Q. Okay. Let's go down to the "Mucosal Immune Responses" section under "Pathogenesis."
A. Sure.
Q. It says, "In patients with celiac disease, immune responses to gliadin fractions promote an inflammation reaction, primarily in the upper small intestine, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy."
Do you agree with that statement?
A. Yes, or at least that's what's thought.
Q. Is that a statement of mechanism at some level?
A. Well, I think what it says is that, and what we think, is that portions -- breakdown products of gliadin are triggers, so in that sense it's the initiation of a mechanism that activates processes that presumably already exist.
Q. Let's go to the second page of this article, Page 1732, there's -- just above the

Page 148

heading "Genetic Factors," there's a sentence just above that, it says, "The mechanism of the interaction between the processes in the epithelium and lamina propria has not been elucidated."
Do you see what I just read?
A. Yes.
Q. Even though that mechanism as described there has not been elucidated, nobody would challenge the fact that gluten causes celiac disease, correct?
MR. PARKER: Objection.
A. Well, I think I just said that I don't agree with your terminology.
BY MR. SLATER:
Q. My question is this. Even though the mechanism has not been elucidated as described in that sentence, nobody would question the fact that gluten initiates a process that leads to celiac disease, correct?
A. I think it leads to symptomatology in celiac disease. If you have celiac disease, stop taking gluten, you feel completely better, do you still have celiac disease? The answer

Page 149

would be yes. So gluten is not necessarily causing the disease or initiating the disease.
Q. You're saying somebody can have the genes for celiac, but the gluten is what actually, in some of those people will actually cause the person to have the symptoms --
A. Yes.
Q. -- associated with celiac, right?
A. Right. That's different than mechanism.
Q. Let's go down to the "Genetic Factors" section, the second sentence. "Celiac disease does not develop unless a person has alleles that encode for HLA-DQ2 or HLA-DQ8 proteins, products of two of the HLA genes."
Do you agree with that statement as being factually accurate?
A. I think that's generally true.
Q. It then says, "However, many people, most of whom do not have celiac disease, carry these alleles; thus, their presence is necessary but not sufficient for the development of the disease."
Do you see what I just read?

Page 150

A. Yes.
Q. And I think -- rephrase.
One of the things that's necessary for the development of the disease is exposure to gluten, correct?
A. Again, I think that's a semantic argument. I think gluten certainly induces the activation of processes that manifests as the disease, but I don't think that's what they're talking about here.
Q. Okay. Let's go to the next page, "Clinical Manifestations." On Page 1733, under "Clinical Manifestations," the article states, "Clinical manifestations of celiac disease vary greatly according to age group."
Do you see what I just read?
A. Yes.
Q. Do you agree with that statement?
A. Yes.
Q. Even within various age groups, the clinical manifestations vary, correct?
A. Yes.
Q. Celiac disease is not a homogenous disease entity, there is variation, correct?

Page 151

A. There is variation in severity and -- yes, severity primarily.
Q. There's a variation in terms of the clinical symptoms, there's a variation of severity, and there's even a variation in the histopathology, correct?
A. Again, the severity, yes.
Q. Celiac disease has heterogeneity in terms of its presentation, correct?
A. Well, again, I think it's what we just said. It has heterogeneity in terms of the severity of presentation.
Q. Even though there's this heterogeneity and this variation in presentation and severity, nobody would challenge that celiac disease is a clinical entity, correct?
A. Can you make that a simpler question?
Q. Sure.
A. You've asked about five different questions there.
Q. I don't think I got to five, Doctor, but thanks for the credit. If I could do that in so few words, then I would be a master questioner --

Page 152

A. Well done.
Q. -- like Mr. Parker to your right, but I'm not. I'm a novice here, and this is my first deposition. Thank you for your patience.
Doctor, celiac disease is a recognized clinical entity, even though there's variation in the clinical presentation in terms of symptoms, in terms of severity, correct?
A. Yes.
Q. Now, looking at Page 1733, at the top of the second column, the first -- second full sentence, it says, "The classic presentation in adults is diarrhea, which may be accompanied by abdominal pain or discomfort. However, diarrhea has been the main presenting symptoms in less than 50 percent of cases in the past decade. Other, silent presentations in adults include iron-deficiency anemia, osteoporosis, and incidental recognition at endoscopy performed for other reasons, such as symptoms of gastroesophageal reflux. Less common presentations include abdominal pain, constipation, weight loss, neurologic symptoms, dermatitis herpetiformis, hypoproteinemia,

Page 153

hypocalcemia, and elevated liver enzyme levels."
What I just read, you agree that is accurate factually, correct?
A. Yes.
Q. Despite that variation in clinical presentations, celiac disease is a recognized clinical entity, correct?
A. That's a variation in symptomatic presentations. All of these patients have a spectrum of the same histopathology and the same pathophysiology. So you're talking about severity again, and so the answer is yes.
Q. We're also talking -- rephrase.
The authors are also talking about variation in the symptoms, and essentially very wide variation in symptoms, correct?
A. No, I think these are symptoms that all relate directly to the malabsorption, so I wouldn't call it wide variation.
I guess I should correct myself. Dermatitis herpetiformis is probably not due to the malabsorption, it is probably due to the immune reactions.
Q. Is abdominal pain due to

Page 154

malabsorption?
A. I think it probably is.
Q. Is constipation due to malabsorption?
A. I think it may be.
Q. You said all of these symptoms relate to malabsorption. Does that include constipation?
A. I answered. I said it may be.
Q. When you say it may be, are you saying yes or no?
A. I would say constipation is an atypical presentation of malabsorption, but there does end up being increased bulk, and that may give patients that feeling. So it would be highly atypical, and along that spectrum they do say that that's a less common presentation. So constipation wouldn't be what you'd normally expect in somebody with celiac disease, but I suppose it's possible.
Q. You would admit there are some patients who have constipation as a result of malabsorption, correct?
A. That's what they're implying here, and I take that at face value.

Page 155

Q. You don't dispute it, correct?
A. No, I don't dispute it. I'm saying it's an unusual pathophysiology of malabsorption. But they're listing it, they're making generalizations here, I don't think I've read reference 35. But the fact is that we're picking up celiac disease cases at higher and higher rates due to increased screening and recognition and serologic assays, and I'm not surprised that some patients that present with constipation are later found to have celiac disease.
Q. This relation of symptomatology as described here, the literature on olmesartan also reflects a similar variation in symptomatology, correct?
A. Again, the symptoms are highly overlapping. I think there's a difference. I don't see vomiting included here. It does seem to be somewhat broader for olmesartan.
Q. In essence what I'm driving at, is the fact that there is a broad spectrum of clinical presentations similar to this spectrum that we're reading about for celiac, that in and of

Page 156

itself does not disprove that olmesartan enteropathy exists as an entity, correct?
A. Can you break that up?
Q. Probably not. Sounds difficult. I'll ask it again.
The fact that olmesartan enteropathy as reported has a similar broad spectrum of clinical manifestations as reported in the literature, that in and of itself does not disprove the existence of olmesartan enteropathy as an entity, correct?
A. Okay. So you've made two statements there. I'll answer them separately if you can't break them up.
The first is the fact that it has a similarly broad presentation, I think it has a broader presentation.
The second is that that doesn't disprove that olmesartan could cause enteropathy, and I would agree with that.
Q. Go to the bottom of Page 1733. It says "Diagnosis." It says at the very bottom, "The diagnostic criteria developed by the European Society for Pediatric Gastroenterology

Page 157

and Nutrition require only clinical improvement with the diet," referring to a gluten-free diet, "although histological improvement on a gluten-free diet is frequently sought and is recommended in adults because villous atrophy may persist despite a clinical response to the diet."
Do you see what I just read?
A. Yes.
Q. If I understand that correctly, they're saying you'd like to see histology on pathology specimens, but according to this standard, this diagnostic criteria cited by the articles, you can make the diagnosis simply on clinical improvement with a gluten-free diet. Am I reading that correctly?
A. They're saying that the European Society says that. I think they're in the minority there. I think most society recommendations would be that you need further evidence than improvement on a gluten-free diet. I think -- and especially since 2007, it's increasingly recognized that there are people who have some sort of gluten sensitivity who do

Page 158

not have celiac disease. So I would say no, I don't think that's what's accurate.
Q. Do the authors criticize that criteria, diagnostic criteria?
A. They don't make a comment either way. But again, you need to recognize that this is almost a ten year old paper.
Q. You cited this in your reliance list as something that was relevant, right, today? Right? That's why you put it on the documents list, correct?
A. I think it provides helpful facts. But I think it also has to be recognized in that context. I didn't say it was authoritative.
Q. Let's go to Page 1735 under "Biology and Histologic Assessment." The last full paragraph in the left column. It says, "The spectrum of pathologic changes in celiac disease ranges from near-normal villous architecture with a prominent intraepithelial lymphocytosis to total villous atrophy."
Do you agree that's an accurate statement?
A. Yes.

Page 159

Q. And even though there is this spectrum of pathology changes that can be seen, that does not take away from the fact that celiac is a recognized and accepted entity in the scientific community, correct?
A. I think describing it as a spectrum is probably overstating your case. There's a constant finding there, which is the prominent intraepithelial lymphocytosis. The variation is the degree of villous atrophy which reflects severity. So I think you're trying to imply that there's this huge spectrum, and there's not.
Q. There has been a reported spectrum of pathology from normal or near-normal villous architecture through total villous atrophy and with other features as well in the literature about olmesartan, correct?
A. There's been descriptions of completely normal histology without anything, including intraepithelial lymphocytosis, on the benign -- on the very bland end to ulceration with neutrophils on the very severe end. Both of those -- neither of those would be considered

Page 160

adequate for a diagnosis, for example, of celiac disease. That's too broad.
So that's my point, is that you're trying to imply a broader spectrum of the type that's been described for olmesartan and celiac disease, while the pathology of celiac disease is not characteristic -- it is not, I'm sorry, diagnostic, the typical or characteristic findings are a much narrower spectrum than has been described with olmesartan.
MR. SLATER: Move to strike.
Q. There is a spectrum of histopathology reported in the literature regarding olmesartan, correct?
A. Yes.
Q. In and of itself, that spectrum as described is not sufficient to reject the existence of olmesartan enteropathy, correct?
A. Correct.
Q. Look at the very bottom of the left-hand column on 1735 over to the carryover, it says, "The diagnosis is confirmed when there is a favorable response to the diet."
Do you see that?

Page 161

A. Yes.
Q. That's a very clear statement by the authors that the way you confirm the diagnosis of celiac disease is by putting the person on a gluten-free diet, and the person improves or gets better, that's what they're saying, correct?
A. That's in the context of all the things above. But yes.
Q. That statement is consistent with those who, from a clinical perspective, believe that if you do a dechallenge of olmesartan and the patient gets better, that that is enough to make the diagnosis of olmesartan-associated enteropathy, they're saying the same thing, correct?
A. I think in a subsequent paper Dr. Green actually specifically says that a clinical response to gluten withdrawal is not sufficient to make a diagnosis of celiac disease.
Q. Do you want to show me that article?
A. Sure.
Q. We'll hold on that. We'll get back to

Page 162

that. I just don't want to take time looking for it, but I'll make a note.

With regard -- and I'm going to move to strike.

With regard to my question, there are clinicians who treat olmesartan enteropathy who believe that if the patient improves and then gets better after withdrawal of the olmesartan, that is enough to make the diagnosis and to make the treatment decision going forward to keep a person off olmesartan, that in the medical community, in the clinical community, there are people that believe that and treat patients based on that, correct?

MR. PARKER: Objection.

A. I can't tell you what they believe.

BY MR. SLATER:

Q. You don't know what the thinking is within the clinical community about that question?

A. I can tell you what articles have been written, what articles say. I'm sure you can find clinicians who think lots of things that are inaccurate. I can tell you what's

Page 163

interpretable as fact, what's interpretable as observation, phenomenon. I can't tell you what people are thinking and whether it's accurate.

MR. SLATER: Move to strike.

Q. Do you not know what the thinking is among those who actually treat and diagnose olmesartan enteropathy in the clinical community, for example, at major institutions where celiac is treated?

A. Yeah, you know, University of Chicago where I was until recently is one of those institutions with a celiac center, and I would say that what is recognized is that in some patients, withdrawal of olmesartan seems to be associated with improvement. Those patients typically had negative celiac serologies and don't have celiac disease by any variety of measures. And that if withdrawal is correlated with a response, then you should just take them off of olmesartan.

Q. And the doctors at the University of Chicago celiac center who had that understanding -- rephrase.

And the doctors at University of

Page 164

Chicago who followed that line of thinking in their medical judgment, you're aware, thought that in those cases the person's gastrointestinal illness had been caused by the olmesartan, and that's why they chose to keep the patient off the olmesartan after the positive dechallenge, correct?

MR. PARKER: Objection.

A. I haven't had that conversation with them, but I can speculate, if you'd like.

BY MR. SLATER:

Q. Well, that's your understanding, that's the only reason they would keep the person off the olmesartan, right?

A. No.

Q. I'll ask it differently. Well, let me ask you this.

Do you know or not know whether they made that judgment as to the fact that the olmesartan was causing the symptoms, and that's why I'll tell the patient don't take the olmesartan anymore. Do you know?

A. You know, the physicians treating celiac disease at University of Chicago are

Page 165

mostly scientifically rigorous people, and I would anticipate that if you ask them, they would say I don't know that it's causing it, but I know that the patient does better when they're not on it, and I can find an alternative, and so I can make this patient better, and that's what my goal is.

Q. Do you know if any of those scientifically rigorous doctors at University of Chicago have published and set forth their thinking on whether olmesartan causes this condition?

A. I'm not aware of any. There's a pretty niche area, and I'm not aware of any papers by any University of Chicago physicians.

Q. Go to Page 1736, please. It's in the section that's titled "Treatment." The third full paragraph right in the middle of the left column, it says, "The elimination of gluten usually induces clinical improvement within days or weeks, though histologic recovery takes months or even years, especially in adults, in whom mucosal recovery may be incomplete."

Is that an accurate statement?

Page 166

A. Yes.
Q. The variation in the time to histologic recovery, that in and of itself can exist, and people still accept that celiac disease is a recognized scientific entity, correct?
A. Yes.
Q. The fact that the histologic recovery in patients who are thought to have olmesartan enteropathy can vary as reported in the literature, that in and of itself does not disprove the existence of olmesartan enteropathy, correct?
A. Correct.
Q. Go to the "Summary," please, the very end, Page 1740. The summary says, "Celiac disease occurs in nearly 1 percent of the population in many countries. The diagnosis, which is straightforward in most cases, is usually established on the basis of serologic testing, duodenal biopsy, and observation of the response to a gluten-free diet."
Do you see that?
A. Yes.

Page 167

Q. With regard to olmesartan enteropathy and the diagnosis of that condition, it is stated in the literature that if the patient has negative serologic testing for celiac, and if you see changes in the villous architecture on the biopsy, and when you withdraw the olmesartan the patient improves or gets better, that is sufficient to make the diagnosis of olmesartan enteropathy, correct?
A. I'm not sure that I've seen a paper state that. I think probably several case reports try to imply that. If there's a paper that says that specifically in those terms, I'm happy to be shown it.
Q. You're not familiar with the paper that suggests that?
A. I'm not familiar with the paper that says that in those specific terms, and if it did I would disagree with it, and I can give you examples of why.
Q. Are you aware that there are physicians who actually diagnose and treat both celiac and olmesartan enteropathy and related conditions who believe that if you rule out

Page 168

celiac with serologies, you see villous atrophy, whether partial or total, on biopsy, and the patient improves or has resolution with withdrawal of olmesartan, that that's enough to make the diagnosis, are you aware that there are clinicians who believe that who are at the pinnacle of the treatment of these conditions?
MR. PARKER: Objection.
A. I doubt there's anyone at the pinnacle. I'm sure you can find people at august institutions, even at celiac disease centers, who will say that. But I think anybody with any common sense would have to reject that you haven't sufficiently ruled out other causes in your scenario.
BY MR. SLATER:
Q. Just to be clear in the context of what you said, you've actually never participated in the diagnosis or treatment of an olmesartan-associated enteropathy patient, whether proven or whether suspected or considered, right?
A. That's true.
MR. SLATER: I think it's a good time

Page 169

to get lunch. Do you guys agree?
MR. PARKER: We agree.
MR. SLATER: Let's break.
MR. PARKER: All right.
THE VIDEOGRAPHER: Going off the record. The time is 12:38.
(Whereupon, a luncheon recess was taken.)

Page 170

AFTERNOON SESSION

(Whereupon, Turner Exhibit Number 13, Setty, et al article titled Distinct and Synergistic Contributions of Epithelial Stress and Adaptive Immunity to Functions of Intraepithelial Killer Calls and Active Celiac Disease, was marked for identification.)

THE VIDEOGRAPHER: Back on the record. The time is 1:26.

BY MR. SLATER:

Q. Doctor, we've provided you Exhibit 13, which is a paper that you co-authored along with Dr. Murray, correct?

A. Well, yeah, I guess.

Q. Were you -- well, let me ask you then, why are you listed as one of the -- were you an author, investigator? What was your role with this study?

A. The reason I hesitated is I'm one of the corresponding authors that directed the study. Joe was a collaborative because he

Page 171

provided patients. So Joe was a co-author. I wouldn't normally think of the senior investigators as co-authors. That's a semantic academic thing.

Q. Looking at the article, it has to do with celiac disease, correct?

A. Yes.

Q. The very beginning of the article, it says, "The mechanisms of tissue destruction during the progression of celiac disease are poorly defined. It is not clear how tissue stress and adaptive immunity contribute to the activation of intraepithelial cytotoxic T-cells and the development of villous atrophy."

Is that a true statement?

A. Yes. Your quoting isn't quite precise, but it's fine.

Q. You mean I didn't read it correctly?

A. Yeah.

Q. I didn't read it correctly?

A. I'm sorry?

Q. I didn't read the sentence correctly?

A. No, you didn't.

Q. All right. I'll try it again then.

Page 172

Doctor, looking at the first sentence of the article, it says, "The mechanisms of tissue destruction during progression of celiac disease are poorly defined. It is not clear how tissue stress and adaptive immunity contribute to the activation of intraepithelial cytotoxic T-cells and the development of villous atrophy."

Did I read that correctly?

A. Yes.

Q. Is it a true statement?

A. What?

MR. TURNER: You're breaking up, Adam.

BY MR. SLATER:

Q. Is it a true statement?

A. Yes, it's a true statement.

Q. Looking at the right-hand column of that page, the first page of the article, the end of the first paragraph, it says, "The mechanisms underlining the licensing IE-CTL to kill IECs are not completely understood, and whether and how adaptive anti-gluten immunity impacts the ability of IE-CTLs to induce villous atrophy remains to be determined."

Do you see what I just read?

Page 173

A. Yes.

Q. Did I read it correctly?

A. Yes.

Q. Is it a true statement?

A. Yes.

Q. Even those these mechanisms that I just read about from your article are not, as you state, completely understood, or remain to be determined, or are poorly defined, that doesn't mean that celiac disease does not exist as a recognized scientific entity, correct?

A. Correct.

Q. These mechanisms that are being discussed, are these mechanisms at the molecular levels?

A. In this study?

Q. What I just read, yes.

A. What you just read were introductory general statements.

Q. Are they general statements regarding molecular level mechanisms?

A. They apply to that, yes.

Q. So you agree you do not need to understand mechanisms at the molecular level to

Page 174

be able to state that there is a plausible biological mechanism for a disease entity such as celiac disease in order to recognize the disease as scientifically accepted, correct?

A. Correct.

Q. And the same would hold true for olmesartan enteropathy, the fact that the molecular mechanisms are still being studied does not mean that the entity does not exist, correct?

A. Correct.

Q. You can put that aside.

I'd like to speak, if we could, for a few minutes about the ROADMAP Study. I think you talked about that, mentioned it in your report, correct?

A. Yes.

Q. The ROADMAP Study, do you know what the primary endpoint was for that study?

A. You're talking about the 2011 New England Journal article?

Q. Correct.

A. The primary endpoint was the time to first onset of microalbinuria.

Page 175

Q. Did you read a study design?

A. There was a previous publication on the study design. I don't know if I included it in my list, and I may not have a copy here. But there was a previous completely separate publication describing the study design in detail.

Q. Did you read that?

A. I did. Some time ago, but I did.

Q. The study was not designed to study gastrointestinal adverse effects, correct?

A. That was not the primary endpoint.

Q. Do you agree the study was not designed in order to study gastrointestinal side effects?

A. It was not designed to primarily determine side effects, but there was certainly an element of the study that they were able to do that because of the large population they studied.

MR. SLATER: Move to strike.

Q. Very simple question. The ROADMAP Study was not designed to study gastrointestinal side effects, correct?

Page 176

A. The ROADMAP Study was intended to be able to also assess side effects. That's the point of large studies like this. That's one of the outcomes that you can measure. It's not the primary outcome, not the primary endpoint, but it's certainly something you can measure, they have tables about it in the paper.

Q. Do you know what the company's position is as to whether or not the ROADMAP Study, which they funded, was designed to study gastrointestinal side effects?

A. Are you going to continue to use gastrointestinal specifically? Because that changes things a bit.

Q. I'm asking you about gastrointestinal.

A. I don't know how they could have, given that this study was published in March, 2011, which means the design was several years earlier before anybody had any thought that there was any association or relationship whatsoever between olmesartan and gastrointestinal disease. So how could you possibly do that?

Q. Do you know when the company began to

Page 177

receive adverse events indicating patients suffering severe gastrointestinal side effects -- rephrase.

Do you know when Daiichi began to receive adverse event reports showing that patients taking olmesartan were suffering for symptoms such as severe diarrhea, significant weight loss, hospitalizations? Do you know when the company started seeing those symptoms being reported in patients taking olmesartan?

MR. PARKER: Objection.

A. My understanding is that there are reports of celiac disease in patients taking olmesartan beginning several years before this.

BY MR. SLATER:

Q. I didn't ask about celiac. I asked about a constellation of symptoms such as severe diarrhea, significant weight loss, the need for multiple hospitalizations. Do you know when adverse event reports indicating that clinical picture for patients taking olmesartan started to come into the company?

A. I couldn't tell you when adverse event reports with that clinical picture started

Page 178

coming in, no.
Q. Once the company saw multiple, and I'll say ten, reports indicating a syndrome of significant gastrointestinal effects including severe diarrhea, significant weight loss, hospitalizations, once they saw more than ten adverse event reports, that's something you would expect them to start to look at and wonder why are we getting these reports, right?
MR. PARKER: Objection.
A. I think they would reasonably be expected to look at that and ask.
BY MR. SLATER:
Q. And if they knew about that at the time that they designed the ROADMAP Study, that's something that they would have had the ability to build into the study if they chose to, right, to study those types of effects, right?
A. If they thought they were significant, I mean certainly they'd have the ability. But you're talking about MedWatch reports, I assume, is that true?
Q. It is.

Page 179

A. That level of data?
Okay. So MedWatch reports are really sort of the lowest quality of data you can imagine. They're vague. There's no proof needed. The estimation of causative relationship is really, you know, a weak estimate at best. It's essentially if you can't prove -- if you can't definitively say no, then you say yes.
So I'm sure they considered that when they designed the study. I wish I had the paper with the details of the study design. But I don't know why, based on that, they would specify gastrointestinal defects, because my understanding is that the incidence was actually lower than in the placebo groups, and I think that's what you see here.
Q. We'll get to that. We'll get to what the study showed, I promise you. Actually, let's deal with what you just said real quick. Actually what they -- rephrase. We will come back to that later.
You're talking about the letter that the two investigators wrote to the Mayo Clinic

Page 180

Proceedings, right?
A. No. I was actually talking about what they designed in advance. But there is that letter, and that letter is relevant.
Q. Let's talk about a couple things, because you said a few things that we want to go through now.
First of all, you have never worked at a pharmaceutical company, right?
A. No, I have not.
Q. Do you know what level of importance pharmaceutical companies who are regulated by the FDA are supposed to pay to MedWatch reports as they come in to the company, or adverse event reports as they're made to the company?
A. I couldn't cite, you know, policy to you. I could tell you that I would, as a layperson in this area, suspect that they should place high importance on them for what they are.
Q. As adverse event reports came into Daiichi regarding patients with a constellation of symptoms such as severe diarrhea, vomiting, dehydration, significant weight loss, hospitalizations, do you understand that the

Page 181

company was supposed to take those adverse event reports very seriously?
MR. PARKER: Objection.
A. That would be my general understanding, but again, not as an expert.
MR. SLATER: Move to strike from "but" forward.
BY MR. SLATER:
Q. You don't hold yourself out as an expert with regard to how adverse event reports are utilized, correct?
A. No, I do not.
Q. And you didn't form any opinions based on adverse event reports in this case, correct?
A. I looked at some adverse event reports, and I factored those into my analysis, yes. You're asking a different --
Q. I thought you only saw those reports a week ago.
A. Well, the MedWatch reports. Case reports are essentially the same thing --
Q. Okay.
A. -- published in a different format.
Q. You equate -- I'm sorry.

Page 182

You equate a case report to an adverse event report, and vice-versa?
A. No, that's not what we were talking about.
Q. I thought you just said that you saw case reports, which are essentially analogous to adverse event reports.
A. No, I said case reports are reports of adverse events. That's not a MedWatch report. MedWatch reports are also reports of adverse events. But I would hope that there's more detail in a case report, in many cases there is not, in many cases the data provided in the case reports is less, but there's a different process, and they are different items.
Q. Do you have an understanding of the concept of power in a clinical study, in RCT for example?
A. Yes.
Q. Do you have an opinion as to whether or not the ROADMAP Study was adequately powered to study adverse events, adverse effects from olmesartan?
A. I understand the concept of power

Page 183

analysis, but I think those statistical details are outside my area of expertise.
Q. You have no opinion on that question, correct?
A. I have no opinion on that question.
Q. Do you know what Daiichi's position is as to whether or not the ROADMAP Study was adequately powered to study adverse drug effects, including gastrointestinal effects? Do you know what Daiichi's position on that is?
A. No.
Q. If the ROADMAP Study was not adequately powered to study any adverse effects, including gastrointestinal adverse effects, that would be significant, right?
A. Sure.
Q. You don't know the answer to that question, though, right?
A. I don't know the answer to that question. I know it was a pretty huge study.
Q. If the ROADMAP Study was not adequately powered to study adverse effects such as gastrointestinal side effects, then you would not want to rely on the ROADMAP Study to form an

Page 184

opinion one way or another on the question of whether olmesartan is associated with sprue-like enteropathy, correct?
A. Well, I think you could rely on it to say there's insufficient data if you assume that it was underpowered, and that, you know, a qualified statistician has proven that.
Q. When you say "insufficient data," you mean if it's underpowered it's not going to give you reliable information on that question, right?
A. Right.
Q. I think I might have touched on this with you before, but I want to be very explicit. You don't know whether there were any adverse event reports generated by the -- rephrase.
You don't know whether Daiichi generated an adverse event report or reports regarding ROADMAP Study patients in the olmesartan arm reporting gastrointestinal side effects? You haven't seen those, correct?
A. I haven't seen those.
Q. And you don't know if there are any such adverse event reports in existence in which

Page 185

a patient had both a dechallenge and a rechallenge, and based on the rechallenge the company and the investigator both found that the gastrointestinal side effects were definitely related to the use of olmesartan, you don't know if that exists, right?
MR. PARKER: Objection.
A. Are we talking about MedWatch reports and that level?
BY MR. SLATER:
Q. We're talking about a MedWatch report generated by Daiichi based on a study participant in the ROADMAP Study in the olmesartan arm.
A. I don't think MedWatch reports are of the level of proof that you're implying. I don't think they confirm that something was definitely caused by. I do think you have to check caused by or not caused by. And my general understanding is that if someone anywhere in the chain says I think this might have been caused by, then that dominates and you can't undo that in order to prevent hiding of cases.

Page 186

So I think, I'm sure there are MedWatch reports where the caused by list -- the caused by is checked and there were dechallenge and rechallenge, I've seen those in tables from some of the reports I've seen. I don't think that constitutes medical proof, and I don't think anybody would hold it up to be.

Q. Who told you that the standard is what you just said for whether or not the company physicians would find something related? Where did you get that information from?

A. You know, I think that sort of understanding was in medical school, that these sorts of adverse reaction reports are really the lowest threshold, and the point is to catch everything and not miss something that's possible, not to prove what's true.

Q. Do you know if in any cases the adverse event reports were evaluated by physicians working at Daiichi who were actually performing a differential diagnosis and applying medical judgment? Do you know if that would occur?

A. I don't know if that would occur.

Page 187

Q. You're assuming it didn't occur, right?

A. No, I'm not making any assumption.

Q. You don't know one way or the other?

A. I mean I'd like to assume that it did occur, but I don't know.

Q. The letter by Manne and Hallar to the Mayo Clinic journal, did they state that there were any MedWatch -- rephrase.

Did Manne and Hallar in their letter to the Mayo Clinic journal provide any information indicating that before they submitted the letter they circulated it within Daiichi for review?

A. They do list potential competing interests. They do not say that they circulated it.

Q. If it the manufacturer of olmesartan, Daiichi, actually had a chance to review that letter before it was submitted for publication, is that the kind of thing that you would expect to be disclosed?

A. I think they disclosed their competing interests. If a member of Daiichi was an

Page 188

author, I think that needs to be disclosed, if they were doing it as part of their paid work for Daiichi. This doesn't say that. These guys both apparently have appointments at the Hanover Medical School, and so I think what they've done is correct as long as it's inclusive. I'm in no position to assess whether they were inclusive, or accurate, or inaccurate.

Q. If the authors of this letter to the editor submitted it to Daiichi in draft form, and Daiichi actually added language to the letter, should that be disclosed?

MR. PARKER: Objection.

A. You know, I think as a funder of the original ROADMAP Study, which I think is true, then Daiichi generally would -- in most cases the drug company would have a right to see the letter before and possibly suggest edits, but it's ultimately the responsibility of the authors.

BY MR. SLATER:

Q. The question is very simple. If Daiichi had input into this letter, that's something that should have been disclosed,

Page 189

right?

A. If Daiichi had -- I mean it depends. What did they do?

Q. Added language suggesting that there's no association, how about if they added that language to the letter?

MR. PARKER: Objection.

A. Was there language like that already in the letter?

BY MR. SLATER:

Q. No, no. Let's assume that the letter was sent to Daiichi in draft, and then after Daiichi reviewed it that language ended up in the letter, you'd want to know that, right?

A. What did it say before that?

Q. It didn't say that at all. That sentence wasn't there. It just found its way into the letter after Daiichi reviewed it.

A. So before that, throughout the letter it said we have no idea whether olmesartan causes this or not, but here are results?

Q. If the company saw the letter and their input resulted in Manne and Hallar saying that they don't believe there's an association,

Page 190

that should be disclosed, right?
A. I think it is by saying that they -- I mean you -- generally the authors take responsibility for what's written. It is true that we often show them to other parties for advice, people who are knowledgeable in the area. Usually that goes in acknowledgements, and that might be there. But this isn't a paper. It's a letter to the editor. So you're really restrictive what you can say. I think they disclose competing interests.
If a ghostwriting at Daiichi wrote the entire thing for them, that should have been disclosed. Was that policy in 2012 at Mayo Clinic Proceedings? I don't know. Different journals have different policies, and that's something that has gradually been increasing, the expectation of that transparency. Let's recognize this is a letter to the editor, there's not a lot of room, and the editors are not going to allow you to put an additional page of notes attached to it.
They've disclosed that they have received money from Daiichi as lecturers and to

Page 191

support research grants. Unless Daiichi rewrote it, I think that's probably not unreasonable, what they've done.
Q. So when it was disclosed at the end of this that both Manne and Hallar have been paid by Daiichi, you think that is also communicating to readers that the letter was submitted to Daiichi in draft? And look in the second paragraph on the first page, halfway down the second column, the sentence, "We detected no association between treatment with 40 milligrams of olmesartan once daily and the occurrence of intestinal adverse effects in 2232 patients treated for a median of 3.2 years in the ROADMAP Study." You think that if the company had that sentence added, you think that's disclosed by them saying we get paid by the company as consultants basically?
A. No.
Q. Is that really what you're saying, Doctor?
A. That's not what I'm saying. I guess, looking at the data in their table, if they hadn't had a sentence like that in there, I

Page 192

would think that they really didn't do a very good job writing this, because that's the take-home message. So I can imagine --
Q. It's --
A. Can I finish?
Q. If it's an underpowered study --
A. Can I finish?
Q. -- it's not the take-home message, because you can't answer the question if it's underpowered, right?
MR. PARKER: Finish your answer.
A. Can I finish my answer?
BY MR. SLATER:
Q. Go ahead, Doctor. I'm going to strike it, but you go ahead.
A. Okay. So if, for example, this statement, "However, our observation of a large group of diabetic patients" was not there, but somewhere else, because all through the next column they talk about how it didn't come out in any of their tests, I think then you would be unreasonable to say if the company recommended putting it there where the content already existed elsewhere, is that the company

Page 193

manipulating, which I believe is what you're driving at.
If the data showed that there was an effect, and the company manipulated the data to not show that, clearly that's wrong, and that shouldn't have been.
But these guys have staked their reputation on it, and they've disclosed that they have potential competing interests. Unless somebody from the company wrote this, I think they've done their duty.
Q. So it's good enough -- I'll withdraw that.
So you, who has all this involvement with medical journals, would find if a journal article was submitted to one that you're editing or peer-reviewing, and you weren't told that the actual sponsor of the study, the manufacturer of the drug under study, had reviewed and had input into the manuscript, you're fine if you don't get told that, and it's passed off as if it was independently written by the study investigators? You're fine with that, is that what you're telling the jury and all the doctors

Page 194

in the country that you know?
A. I think you're stretching that to an extreme, and I would not agree with the way you've stated things.
Q. Please, it's a yes or no question. Tell every doctor in the country that you know right now, yes or no, you're okay with that, please.
A. Okay with what? Can we be specific?
Q. You heard the question.
A. Can you read it back?
Q. I'll ask it again.
You're okay as an editor of medical journals, a peer reviewer, when somebody is writing an article about a study where the sponsor of the study who manufactured the drug being studied had input into how the article was written, and that's not disclosed to you, and the investigators who submit the article act as if they wrote the article entirely independently, you're fine with that?
A. It depends on the level of input.
Q. Changing the language in the article?
A. Changing the language, or the meaning?

Page 195

Changing the language, or the meaning?
Q. Both, or either one.
A. If they change the meaning, I'm not okay with it. If they make grammatical edits to language, I don't think that's a big deal.
Q. It should be disclosed, though, so that the editors and the peer reviewers can make their own judgment as to whether the changes were material, right?
A. Do you know that it wasn't disclosed?
Q. Do you see any disclosure here?
A. I see a potential competing interest disclosure. When I see something like that on an article at my journal, and I've done this recently, I will contact the authors and ask for more detail if I feel that more detail is needed. And I would assume that --
Q. It's not disclosed here, right?
A. It's not disclosed in what appears in the journal. There's a limit. These are long -- these can be longer conversations with a long e-mail chain. You know, I just had -- I think in a paper I just accepted into our journal, I just had a series of probably six e-mails and a

Page 196

telephone conversation with an author. In the end, I concluded that what they'd written in their conflict of interest statement was sufficient. Is all the detail in those reflected in that? No. It would take another three pages of the journal. Did it require that it satisfy me? Absolutely.
Q. All right. Well, you have a low standard, I guess. It's okay if people just say whatever they want to say, that's fine.
A. Hold on. That's not true. You're calling me somebody with low standards? That's not true.
Q. Okay. That's how it sounds, but I'll move on.
A. You need to listen more carefully.
Q. To the extent that patients were judged by the investigators -- rephrase.
To the extent that ROADMAP Study patients, one or more, were judged to have suffered gastrointestinal affects consistent with sprue-like enteropathy that were definitely related to the use of olmesartan, and that that judgment was made both by an investigator and by

Page 197

the company physician reviewing the adverse event, that information should have been disclosed in this letter, right?
MR. PARKER: Objection.
A. I don't think definitely came into anything. If a definite decision was made that it was absolutely a cause in the rigorous scientific sense of disease, it should have been disclosed.
BY MR. SLATER:
Q. There's no suggestion that any patients in this study developed symptoms consistent with a sprue-like enteropathy, they don't suggest that or disclose that at all, do they?
A. Well, they do discuss that.
Q. What do they say?
A. They say "This finding might be because sprue-like enteropathy is a rare event. Indeed, the 22 reported cases in the report by Rubio-Tapia, et al came from 16 different states and were diagnosed at the Mayo Clinic during a time frame of three years. We cannot rule out the possibility that in this" way -- "in this

Page 198

very rare disease, the intestinal renin-angiotensin system plays a role." I think they've been up front about it.

MR. SLATER: Move to strike.

Q. That wasn't my question.

My question is, did they disclose anywhere in this letter that there were ROADMAP Study patients, any of them, that had symptoms consistent with sprue-like enteropathy? Did they disclose that here?

A. They disclose that they had patients with features consistent with that and many other things, nonspecific features.

Q. Did they disclose that any patients were determined to have suffered from symptoms consistent with sprue-like enteropathy that were found to be related to the use of olmesartan? Did they disclose that, based on that analysis, that that was found with regard to any patients?

A. That's the whole point of their analysis.

Q. Did they say that, Doctor? Is it in the article? Do they disclose that? Caused by olmesartan, do they say that?

Page 199

A. That's the question they're asking.

MR. SLATER: Doctor, non-responsive. Move to strike.

Q. Do they disclose here that there were any patients where it was determined that olmesartan caused symptoms consistent with sprue-like enteropathy in an olmesartan patient in this study? Is that stated?

A. I don't know how to answer your question because you're trying to conclude that they did a study to ask a question they already knew the answer of. I don't understand.

Q. You don't understand that? I'll try to explain it to you.

Do they disclose in this letter that there were one or more patients who had symptoms that were analyzed by Daiichi and by the investigators and determined that olmesartan caused those sprue-like symptoms in that patient as part of this study, including a patient who had both a dechallenge and a rechallenge which were both positive? Is that disclosed?

MR. PARKER: Objection. Foundation.

A. No, they don't report on individual patients here, so no.

Page 200

BY MR. SLATER:

Q. Do they disclose that there were any patients who had positive dechallenge and positive rechallenge for gastrointestinal illness as part of the olmesartan arm of this study? Do they disclose that?

MR. PARKER: Objection.

A. That's not discussed.

BY MR. SLATER:

Q. If that happened, that should have been disclosed to make this a fair and balanced discussion of this situation, correct?

A. I would say if you want to make this into a full paper, then yes, in the context that patients with similar symptoms, which there were, I think, just as many of or more in the placebo group, depending which conditions you look at, were analyzed in the same way, and you could compare apples and apples.

It's the same problem as the Rubio-Tapia study. It's a great -- it's a great case series to bring people's attention to a potential problem, which I believe is the way

Page 201

they phrase it, but if you set up your study in the Rubio-Tapia case to only include people who were sick and got better coincident with discontinuation of olmesartan, then you're never going to find anybody in that study group who withdrawal olmesartan, a dechallenge as you call it, but I wouldn't agree that it's a controlled dechallenge, but a dechallenge, you'll never find people with negative dechallenge, because you excluded them from your study.

So here they're trying with what is considered the most rigorous scientific approach, randomized controlled trials, yes, they have been to be appropriately powered. But they're trying to use a randomized clinical trial, the most rigorous approach, to detect a signal from gastrointestinal disease, and they are saying that they did not. They're not coming down to the individual patient level, other than to say how many patients in categories.

And I think in a letter to the editor, that's appropriate, I assume that as any academic would do, they took some time and

Page 202

looked at their data and said should we write this as a full paper or a letter to the editor. They apparently thought it wasn't that big a deal, because they sent it to the same journal where it was published, so they just wanted continuity in the literature that, hey, we did this big deal study that was published in the New England Journal, but there was this little report in the Mayo Clinic Proceedings, so we just want to add to the Mayo Clinic Proceedings that we didn't see any.

The threshold for publishing letters to the editor in the Mayo Clinic Proceedings is obviously incredibly low. So there's clearly -- they just wanted to make the statement as an addendum to their data, but that's all it is.

MR. SLATER: Move to strike.

Q. The population of patients in the ROADMAP Study were diabetic, right?

A. Yes.

Q. That's not representative across the board of patients taking olmesartan, because all olmesartan patients aren't diabetic, right?

A. That's true.

Page 203

Q. Diabetic patients can have diarrhea for multiple reasons, correct?

A. That's true.

Q. Based upon the fact that the population of patients in the ROADMAP Study were diabetic, based on the fact that the study was not designed to study adverse effects of the gastrointestinal system, and based on the fact, assuming I'm correct, that the study was underpowered to study adverse effects such as gastrointestinal side effects, the ROADMAP Study does not answer the question at all about whether there's an association between olmesartan and gastrointestinal effects sprue-like enteropathy, correct?

A. If everything you said is true, then that's correct.

Q. What's next.

IBS is short for irritable bowel syndrome, correct?

A. Correct.

Q. The mechanisms for IBS have been postulated, but they have not been fully determined, correct?

Page 204

A. Correct.

Q. Despite that, nobody would deny that there is a clinical entity known as IBS which a patient can be diagnosed with, correct?

A. No, I don't think that's true. I think there are plenty of people who don't think it's a real disease.

Q. There are people who think IBS is just sort of a catchall diagnosis if you're not sure what's going on?

A. Well, it is a catchall diagnosis, and I think everybody, even the highest expert in the field, would agree that it's a nonspecific diagnosis and likely represents multiple diseases.

What I'm saying is that I've certainly run across physicians who think it's just an extreme end of normal and it's not a disease. I don't hold that opinion, but you asked about everybody.

Q. With the clinical presentation that is stated in the literature to be consistent with olmesartan enteropathy, could be misdiagnosed with IBS if the doctor doesn't know about the

Page 205

potential association of olmesartan, that can happen, right?

MR. PARKER: Objection.

A. It depends on the level of evaluation. What most of the reports associated with olmesartan show is some histopathology, and by definition IBS should have normal histology.

BY MR. SLATER:

Q. I'm talking about clinical diagnosis without pathology.

A. Well, then the effects are so nonspecific, so could a viral gastroenteritis. Now you're just talking about very nonspecific stuff. So it could be confused with IBS --

Q. Your patient has not had a biopsy, they could be diagnosed with a whole host of potential gastrointestinal disorders as opposed to olmesartan where the doctor doesn't know to include that in a differential diagnosis, correct?

MR. PARKER: Objection.

A. Again, that's about three questions. You're really good at this. Which ones do you want me to answer, in what order?

Page 206

BY MR. SLATER:
Q. If you don't think you can answer the question, I'll just move on.
A. I can't answer the question as asked. There's about three questions in there.
Q. Okay. Do you know why it is that deliberate controlled rechallenge is generally not attempted in cases where a doctor suspects olmesartan enteropathy?
MR. PARKER: Objection.
A. I know it's written in the articles.
BY MR. SLATER:
Q. Have you ever -- well, rephrase.
And what is written in the articles?
A. Because of the symptomatology associated and the desire not to reinduce that.
Q. Because the doctors have documented in the peer-reviewed literature that they think it's too dangerous to deliberately rechallenge in those cases, right?
A. I don't know if dangerous is the word they use, but they don't want to rechallenge, and as a patient I would agree.
Q. Due to the severity of the symptoms,

Page 207

for example, the doctors at the Mayo Clinic did not deliberately rechallenge, correct?
A. Let me check the terminology they used. I'm missing one. Do we know where the Rubio-Tapia paper went?
MR. PARKER: I didn't take it, so I can't tell you.
BY MR. SLATER:
Q. I'll tell you where it is, Doctor. Have you got the article?
A. No, I can't find the article. That's what I'm looking for.
Q. I'll read it to you. If you want to save time, I'll read it to you, and you can tell me if you trust me.
A. I'll agree with you that to my best recollection that's the terminology they use. Not dangerous, but severe.
Q. I'm going to read to you from Page 735 of the Rubio-Tapia article. It says, "No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although two patients reported anecdotally that their symptoms had

Page 208

worsened when they restarted olmesartan before the potential association was recognized, and two patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and reintroduction of olmesartan."
Is that your understanding of what that article says? I just read it to you. You can double check if you want.
A. I think it's really telling actually, because only two patients -- it's telling you if you read their previous paper, too, that only two of eight patients responded to olmesartan withdrawal, but only the ones who improved were included in the study. It creates a whole lot of confusion.
Q. Actually what they wanted to do was announced that they had found a new entity and wanted to give to the medical community the clearest picture they could give in introducing this to the medical community. That's a reasonable thing for researchers to do, right?
A. I think it's reasonable to announce a

Page 209

potential association, and that's what they did. I don't think they believed that they had discovered a definitive new entity. I think their terminology is very clear on that. And I think if you go back and read their collagenous sprue paper you'll find that they had eight patients there taking olmesartan, then they went back and put these two papers together, they then went back and told all those patients to stop taking olmesartan. Only two were included in the proceedings paper, which implies that six didn't do better.
MR. SLATER: Move to strike. It's not responsive.
Q. Doctor, I understand you want to talk about certain things, and with all due respect you don't have your numbers right, but I'd like to try to stick to my questions.
A. With all due respect, I think my numbers are exactly right, and we can go through the papers if you'd like.
Q. Well, let's do this first.
Will you agree with me that those physicians and researchers who were actually

Page 210

considered to be authorities in this field with regard to celiac disease and related disorders, that they accept that olmesartan causes sprue-like enteropathy in some group of patients?

MR. PARKER: Objection.

A. Again, let's parse that out. I think that people who are experts in celiac disease would agree that there's an association between olmesartan and enteropathy in some patients.

Does that answer your question?

BY MR. SLATER:

Q. Well, it doesn't, but I'll start there.

The question is, those experts believe that olmesartan does cause sprue-like enteropathy, or otherwise known as olmesartan-associated enteropathy, in some number of patients?

MR. PARKER: Objection.

BY MR. SLATER:

Q. That's what the prevailing wisdom is among the experts with regard to this question, correct?

Page 211

MR. PARKER: Objection.

A. I would say I think if they thought that, they wouldn't continue to use the term associated. They would say induced.

BY MR. SLATER:

Q. Let's look at the Cartee and Murray article. Do you have that handy?

A. Yeah. Do you want to pull your copy so it becomes an exhibit?

Q. I don't know if we sent one up, because we figured you'd have all the literature.

MR. PARKER: We've got it if you want to ask questions.

A. I have it.

BY MR. SLATER:

Q. Okay. You're familiar with this article, correct?

A. Yes, I am.

Q. It was authored by Dr. Murray and Dr. Cartee, correct?

A. Correct.

Q. And let's look to the question you just raised. Go to the -- to Page 4 of 8 on

Page 212

Page 420, there's a heading that says "Hypothesized Mechanism."

A. Yes.

Q. Right under that heading it says, "The damage induced by olmesartan is a chronic inflammatory change similar, but not identical, to celiac disease."

Do you see what I just read?

A. I do.

Q. So that's Dr. Murray and his co-author saying that olmesartan causes a chronic inflammatory change similar, but not identical, to celiac disease? That's what that sentence means, correct?

A. That's the implication.

Q. Go to the next page, Page 5 of 8, under "Discussion." It says, "The recently recognized syndrome of OAE initially reported in case series and several case reports is indeed quite rare. The syndrome as reported is clinically severe and may be life-threatening."

Do you see what I just read?

A. Yes.

Q. So even though they're using the term

Page 213

OAE in that sentence, they're clearly stating they believe this syndrome exists, and that it is clinically severe and may be life-threatening when it happens to patients, correct?

A. They're saying -- they're giving it a name and saying that they believe it exists. I don't think they're saying it causes the disease.

Q. They're talking about a syndrome.

A. Right, a syndrome.

Q. Okay. That's a clinical syndrome they're talking about here, correct?

A. They're talking about a clinical syndrome and a drug association, not a drug affect.

Q. When they said "it induces a chronic inflammatory change similar, but not identical, to celiac disease," you agree with me that means that the olmesartan causes this condition, correct?

A. That's under the header of Hypothesized Mechanism. Right above that they comment that one of their patients that they diagnosed as having, quote, OAE, then had a

Page 214

positive tTG and did better on a gluten-free diet. So this paper actually documents how unreliable that diagnosis can be.

Q. Let's give you that for argument sake, that the diagnosis in some patients may be unreliable. You agree with me that in some patients the diagnosis is very reliable, correct?

A. No.

Q. You don't think the diagnosis of olmesartan causing a patient's gastrointestinal syndrome of sprue-like enteropathy is a reliable diagnosis in any case that's ever been reported in the literature?

A. I haven't seen a case that has met scientific rigor of causation.

Q. And that's because it didn't come out of a blinded RCT, is that what you're testifying to?

A. That's because it lacks everything that you expect in something that shows causation. A blinded RCT isn't the only way to show that. But there's nothing here that shows that, other than the anecdotal case reports and

Page 215

coincident disappearance or reappearance of vaguely described symptoms. There's really nothing rigorous here.

Q. Do you think that these researchers like Dr. Murray and the others who have written about what they found with their own patients where they were able to determine that olmesartan was causing the sprue-like enteropathy, do you think they're all wrong and you're right? Is that your testimony for this jury?

A. No, I think they're being very careful to state it like it is. They found an association. But if you go back, they're also on -- they're also on case-control studies which are not as good as randomized controls, but here at least you know everybody in your case group fits your definition, and they couldn't find any evidence there either.

So if you're just basing your conclusions on isolated case reports, I don't care if you have 1,000 of them, case reports that are anecdotal and not properly worked up for that sort of detail can't prove causation.

Page 216

That's all that's here is case reports.

Q. There's not only isolated case reports, are there, Doctor?

A. There's just case reports and small series of 10, 20 patients.

Q. What would you like to do to prove this? Would you like to see somebody actually structure a randomized controlled trial to study this question?

A. You could do that. You could do animal studies. You could do case control studies. You could do controlled dechallenge/rechallenge. There's a lot of things you could do. None of it has been done -- well, some of it has been done. To the extent it's been done, none of it has shown a clear causation.

Q. Okay. Let's start with RCTs.

Who is going to -- how many patients would you need to put into an RCT to study whether or not patients get sprue-like enteropathy from the use of olmesartan? You have no idea how many patients you'd need, right?

Page 217

A. I don't know how many patients you'd need.

Q. If anybody -- rephrase.

Okay. You don't know what the cost of that study would be, right?

A. No, I don't.

Q. Okay. Tell me the study that Daiichi -- I'm going to withdraw that actually. We don't need to go there.

The Cartee article, I want to go through a little bit of detail with you on this before I lose track of it. This article is not talking about the 22 Rubio-Tapia patients, it's talking about a broader spectrum of patients, correct?

A. I believe so. I'm not sure that the Rubio-Tapia -- I think the Rubio-Tapia patients are probably included in here. This is more of a review conversational paper than a database paper.

Q. Go to Page 58, please, the right column, the second full paragraph, it says, "Recognition of OAE as a clinical entity reminds us of several key lessons in caring for